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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/900,220 07/24/97 MIAD

EXAMINER

N CIBT-P01-044

ART UNIT PAPER NUMBER

42

028120 HM22/0625  
ROPE & GRAY  
ONE INTERNATIONAL PLACE  
BOSTON MA 02110-2624

DATE MAILED: BRAUNNOCK, M

1646

06/25/01

**Please find below and/or attached an Office communication concerning this application or proceeding.****Commissioner of Patents and Trademarks**

## Office Action Summary

Application No. 08/900,220	Applicant Miao, N. et al.
Examiner Michael Brannock, Ph.D.	Art Unit 1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

1)  Responsive to communication(s) filed on Apr 11, 2001

2a)  This action is FINAL.      2b)  This action is non-final.

3)  Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle* 1035 C.D. 11; 453 O.G. 213.

### Disposition of Claims

- 4)  Claim(s) 1-35, 39-43, 47-49, 52-71, and 75-79 is/are pending in the application.
- 4a) Of the above, claim(s) 1-34, 41, 47, 48, 55-61, and 71 is/are withdrawn from consideration.
- 5)  Claim(s) \_\_\_\_\_ is/are allowed.
- 6)  Claim(s) 35, 39, 40, 42, 43, 49, 52-54, 62-65, 67, 69, 70, and 75-79 is/are rejected.
- 7)  Claim(s) 66 and 68 is/are objected to.
- 8)  Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9)  The specification is objected to by the Examiner.
- 10)  The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.
- 11)  The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b)disapproved.
- 12)  The oath or declaration is objected to by the Examiner.

### Priority under 35 U.S.C. § 119

- 13)  Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) All b) Some\* c) None of:
1.  Certified copies of the priority documents have been received.
  2.  Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3.  Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \*See the attached detailed Office action for a list of the certified copies not received.
- 14)  Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

### Attachment(s)

- 15)  Notice of References Cited (PTO-892)
- 16)  Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17)  Information Disclosure Statement(s) (PTO-1449) Paper No(s). 41
- 18)  Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 19)  Notice of Informal Patent Application (PTO-152)
- 20)  Other: \_\_\_\_\_

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## **DETAILED ACTION**

### *Continued Prosecution Application*

1. The request filed on 4/11/01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08900220 is acceptable and a CPA has been established. An action on the CPA follows.

### *Status of Application: Claims and Amendments*

2. Claims 1-35, 39-43, 47-49, 52-71 and 75-79 are pending.

3. Applicant is notified that the amendments put forth in Paper 37, 4/11/01, have been entered in full.

4. Claims 1-34, 41, 47, 48, 55-61 and 71 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 19, the traversal having been addressed in Paper 32.

5. Claims 35, 39, 40, 42, 43, 49, 52-54, 62-70 and 75-79 are currently under examination.

### **Formal Matters:**

6. Applicant has submitted new claims 72-76, however claims 72-74 have been previously submitted and subsequently canceled. Applicant is notified that new claims 72-76 have been

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renumbered as 75-79. Additionally, it appears that the intended amendment to claim 35 is incomplete, e.g., compare proposed amendment with marked-up version, see also below in item

***Inventorship***

7. In view of the papers filed 4/11/01, the inventorship in this nonprovisional application has been changed by the deletion of N. Miao, M. Wang, NK Mahanthappa and K. Pang.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of the file jacket and PTO PALM data to reflect the inventorship as corrected.

***Claim Rejections - 35 USC § 112***

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 35-43, 77, 78, and 79 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The amendment to claim 35, as set forth on page 1 of Paper 37, 4/17/01, appears to be incomplete: the phrase “hedgehog amino acid sequence binds to a patched protein or regulates proliferation of testicular germ line cells”, as set forth in the marked up version on page 4,

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appears to be missing. For the purpose of examination, the claim will be treated as if this phrase had been included.

Claim 35, 77-79 require that the amino acid sequence regulate proliferation of testicular germ line cells. The phrase "regulate proliferation of testicular germ line cells" renders the claim indefinite because there is no art recognized definition of the phrase and nor is there any mention of this phrase in the specification as filed.

Claims 35, 39, 40, 42, 43, 49, 52, 53, 54, 63, 69, 70, 77 and 78 require molecular weight values for the protein encoded by the claimed polynucleotide. However, since the measured molecular weight value of a protein varies with the method by which it is measured (e.g. denaturing gel electrophoresis, gel filtration chromatography, or calculation from amino acid sequence), recitation of a value for molecular weight without reference to the method by which it was measured renders the claims indefinite.

In claim 63 the recited term "desert hedgehog" without any reference to a particular amino acid sequence, is indefinite because the instant specification does not identify that material element or combination of elements which is unique to, and therefore, definitive of "Desert hedgehog". An artisan cannot determine what additional limitations are placed upon a claim by the presence of this term.

Claim 77 requires that the nucleic acid encode a polypeptide "consisting essentially of a hedgehog amino acid sequence" which is at least 98% identical to either SEQ ID NO: 17 or an N-terminal fragment thereof. The phrase "consisting essentially of a hedgehog amino acid

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sequence" renders the claim indefinite because specification has not put forth those features that are essential to a hedgehog amino acid sequence, therefore the metes and bounds of the claim cannot be determined

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 35, 39, 40, 42, 43, 49, 52, 53, 54, 62, 63, 64, 65, 69, 70, and 75-79 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid encoding a polypeptide of SEQ ID NO: 17, or fragments of SEQ ID NO:17, does not reasonably provide enablement for polynucleotides that encode amino acid sequence variants of SEQ ID NO: 17, nor for amino acid *sequences* that have any particular function. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 35, 39, 40, 42, 43, 49, 52, 53, 54, and 77-79 require that a "hedgehog amino acid sequence bind to a patched protein". As commonly understood, an amino acid sequence is an abstraction and not a physical entity, i.e., it is a description of a polypeptide, and one of skill in the art would not be able to bind a patched protein with an amino acid sequence. Accordingly,

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replacing the phrase “amino acid sequence” with the word “polypeptide” or “protein” would obviate this part of the rejection.

Claims 35, 39, 40, 42, 43, 63, 65, 69, and 70 require nucleic acids encoding amino acid sequence variants of SEQ ID NO: 17. As set forth in item 4 of Paper 28, the specification does not provide sufficient enabling basis to allow the skilled artisan to *make* a polynucleotide encoding an amino acid sequence variant of the polypeptide of SEQ ID NO: 17 that still retain any asserted properties of the polypeptide SEQ ID NO: 17. Conversely, the specification has failed to teach one of skill in the art how to *use* a polynucleotide encoding an amino acid sequence variant of the polypeptide of SEQ ID NO: 17 that does not have any asserted properties of the polypeptide SEQ ID NO: 17.

Applicant argues on page 6 of Paper 37 that the fragments encompassed by the claims are limited to a specific size and function and thus are not “almost limitless” in number as suggested by the previous Office action. This argument has been fully considered but not deemed persuasive because the claims are directed to a polynucleotide that encodes a polypeptide having at least 98% identity to a 19 KD fragment of SEQ ID NO: 17. As Applicant points out, each of the encompassed polypeptides would have at most four amino acid substitutions relative to SEQ ID NO: 17, however, the claims encompass a “practically limitless” number of such polypeptides, each of which having an amino acid sequence that is different than any other. As set forth previously, the specification provides only a single example of a polypeptide that has at least 98% identity to SEQ ID NO: 17, this example being SEQ ID NO: 17 itself. Further, the

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specification has provided only general guidelines as to how to make and test amino acid sequence variants of SEQ ID NO: 17, and no specific guidance as to which of the almost limitless number of sequence variants encompassed by the claims could be used for any desired purpose. As set forth previously, the effect of amino acid substitution is highly unpredictable, thus one of skill in the art is left to extensive experimentation wherein amino acids are randomly changed, deleted, or added to a polypeptide of SEQ ID NO: 17, and through trial and error experimentation is left to determine when a polypeptide is obtained that could be used. As set forth previously, such extensive random experimentation is considered unduly burdensome.

Additionally, as currently worded claim 64 requires that both the nucleotide sequence of SEQ ID NO: 8 and its complement encode a hedgehog protein, which is impossible because only one strand can encode a polypeptide.

12. Claims 63, 65, 67, 69 and 70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims require an isolated nucleic acid which encodes a naturally occurring Desert hedgehog protein of human origin. The specification discloses a naturally occurring polynucleotide of SEQ ID NO: 8 encoding a naturally occurring polypeptide of SEQ ID NO: 17, yet the claims implicitly require allelic variants of SEQ ID NO: 8 which encode naturally

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occurring polypeptide variants of SEQ ID NO: 8, such polynucleotides are not described in the specification. Although one of skill in the art would reasonably predict that many of these sequences exist, see *Ayala et al.*, Modern Genetics, 1984, page 678, and also EP-874048-A2 which discloses a Desert hedgehog of human origin that differs from SEQ ID NO: 17 by two amino acid positions (see attached sequence alignment), one would not be able make useful predictions as to the nucleotide positions or identities of those sequences based on the information disclosed in the specification. None of these sequences meet the written description provision of 35 U.S.C. 112, first paragraph.

With the exception of the of the polynucleotide of SEQ ID NO: 8, the skilled artisan cannot envision the detailed chemical structure of the encompassed variants. Therefore, only the polynucleotide of SEQ ID NO: 8, and polynucleotides 8 of fragments thereof, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

Applicant argues at page 7 of Paper 37 that one of skill in the art reading the specification at the time of filing would have recognized that Applicants' were in possession of the full scope of pending claims, because the specification shows clear recognition of the structure-activity relationship of hedgehog proteins and demonstrates clear understanding of how amino acids can be replaced with an eye towards retaining biological activity. This argument has been fully considered but not deemed persuasive because the specification discloses only one naturally occurring Desert hedgehog protein from human origin, and there is no description of mutational sites that exist in nature, nor how the structure of SEQ ID NO: 8 relates to the structure of any

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other naturally occurring nucleic acid that encodes what can reasonably be termed a "Desert hedgehog" protein. The claims do not require any structure or function or structure/function relationship between SEQ ID NO: 8 and the multitude of nucleic acids encompassed by the claims.

**Withdrawn Rejections:**

13. The rejection of claims 63 and 67 under 35 U.S.C. 102(b) as being anticipated by Hillier et al., Genome Res. 6(807-828)1996, as set forth in item 8 of Paper 28, is withdrawn in view of Applicants' persuasive arguments in Paper 37.

***Allowable Subject Matter***

14. Claims 66 and 68 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

***Conclusion***

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

*Howard Roman  
Primary Examiner*

MB

*WJ*

June 22, 2001